PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What are the barriers to the completion of a home-based rehabilitation program for patients awaiting surgery for lung cancer: a prospective observational study.
AUTHORS	Catho, Heloise; Guigard, Sebastien; Toffart, Anne-Claire; Frey, Gil; Chollier, Thibaut; Brichon, Pierre-Yves; Roux, Jean-François; Sakhri, Linda; Bertrand, Dominique; Aguirre, Charles; Gorain, Sandy; Wuyam, Bernard; Arbib, François; BOREL, Jean

VERSION 1 – REVIEW

REVIEWER	Catherine Granger The University of Melbourne, Australia
REVIEW RETURNED	31-Jul-2020

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. This is an interesting paper which aimed to identify determinants of noncompletion of a home rehab program and the factors associated with medical events occurring 30-days after hospital discharge for patients undergoing surgery for lung cancer. The design is a single group observational study. The study found that living alone, polypharmacy (likely indicating multimorbidity) and a long delay before starting the rehab program were the main factors associated with the risk of not completing the program. These are very interesting findings. The authors should be congratulated on producing this informative manuscript. This work is important because prehab for patients undergoing surgery for lung cancer appears to be effective, yet because of the very short time frame available before surgery, there are questions around its feasibility. In general, the evidence for prehab in lung cancer has not translated into clinical practice and is not yet routine clinical care in most centres. One potential model is home based exercise – such as is tested in this paper – as this theoretically should be easier for patients to adhere too, for example it minimises barriers such as travel and time to attend a centre based exercise program. I am not aware of other published work looking at the feasibility of the home prehab model in this population and therefore this paper is a good addition to the field. It is informative for people designing RCTs to examine the efficacy of home-based prehab (most RCTs have tested centre based programs instead). A strength of the paper is that it was conducted in a number of hospitals. Overall this is a well written, clear and succinct paper. I only have a few minor suggestions. Minor suggestions:

	- Page 4 line 49 – the terms ‘clinical trial’ – should that be changed to ‘study’ as this is not an RCT? - Page 7 line 2 – the heading ‘quality of life’ here seems strange as the questionnaires you describe under this heading refer to measurement of symptoms of depression, anxiety and fatigue – could they be moved under a different outcome heading? It does not appear like a standard HRQoL questionnaire was used (such as the EORTC QLQ C30 or FACT) which are commonly used in cancer studies.

REVIEWER	M. Janssen-Heijnen VieCuri Medical Centre/Maastricht University The Netherlands
REVIEW RETURNED	26-Sep-2020

GENERAL COMMENTS	This is a well written manuscript on determinants of non-completion of home-based rehabilitation programs (H-RP) before surgery in lung cancer patients and the factors associated with medical events occurring 30-days after hospital discharge. This study is an addition to the development of prehabilitation in patients with lung cancer. The manuscript could be improved by addressing some limitations. Limitations: Abstract: • Please provide information on the duration of the H-RP. • Please provide information on the number of events for each outcome variable and whether factors associated with medical events at 30 days were the results of univariate or multivariable analyses. • In the conclusion, the result on early start of H-RP is missing. Strengths and limitations: • Please describe the possible effect of selection bias on the results. Please also include this information in the discussion section. Introduction: • Please include percentages for the risk of postoperative complications and rehospitalisation (overall and in fragile patients). Methods: • A better description of the population is needed (e.g. what is the period of inclusion, how were patients invited to participate in the study, was there any non-response, etc.). • Information on details of content and duration of the prehabiliation program is missing (this information could also be displayed in a table). What were the components of nutritional intervention and how was measured what was needed in each patient? How long did training sessions last? Which strength exercises, which coaching, homework exercises? Were there any barriers with respect to placing a cycle-ergometer at home/room for exercising? And did patients receive a shedule for home-based cycling? Patients were asked to cycle for 20-40 minutes, but had to reach a minimum of 30 minutes? Did patients fill in a logbook in order to measure completion of components of H-RP? Were all patients supervised by the same physiotherapist from the hospital of was supervision performed by regional physiotherapists?

	• Data collection: 'living situation' is missing; why did the authors limit postoperative complications to medical events after discharge instead of also including events during hospitalisation? And why did the authors not include duration of hospital stay as important outcome measure? • Please include more information on multivariable analyses (forward, backward of stepwise, p-in/p-out). In addition, the multivariable analysis seems to be underpowered. • Given the small sample size, the authors could have used p<0.10 for significance. In the current version of the manuscript, the conclusions/recommendations might be too firm by excluding some factors that might be important with respect to determinants of noncompletion of H-RP and the factors associated with medical events occurring 30-days after hospital discharge. • Reference for the modified Borg scale is missing. Results: • It is not clear how delays were classified (categorized or continuous variable). • The variable 'delay between program initiation and surgery' seems to be missing in the figures. • The manuscript would improve by including information on reasons for non-completion and when in the process non-completion occurred (e.g. first week, last week). In case this information is not available, please include a paragraph in the discussion section. Tables: • Table 2 may clearly state the reasons why participants achieved non-completion; furthermore, how was the completion rate for the full program calculated given the fact that not all patients were referred to all four components of H-RP? Figures: • Please include in the title that results are derived from univariate analyses. Minor comment: • Why is each word in the title capitalized?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Prof. Catherine Granger

Comment # 1 : …..[This work is important because prehab for patients undergoing surgery for lung cancer appears to be effective, yet because of the very short time frame available before surgery, there are questions around its feasibility]….
We thank Pr Granger most sincerely for her general appreciation of our work.

Comment # 2 ; Page 4 line 49 – the terms 'clinical trial' – should that be changed to 'study' as this is not an RCT?
This has been done, thank you.

Comment # 3 ;- Page 7 line 2 – the heading ‘quality of life’ here seems strange as the questionnaires you describe under this heading refer to measurement of symptoms of depression, anxiety and fatigue – could they be moved under a different outcome heading?
We totally agree and propose to replace the term "quality of life" by "patient reported outcomes". This has also been changed in Table 1.

Reviewer: 2 Prof. Maryska Janssen-Heijnen

This is a well written manuscript on determinants of non-completion of home-based rehabilitation programs (H-RP) before surgery in lung cancer patients and the factors associated with medical events occurring 30-days after hospital discharge. This study is an addition to the development of prehabilitation in patients with lung cancer. The manuscript could be improved by addressing some limitations.
We thank Pr Maryska Janssen-Heijnen most sincerely for her general appreciation of our work and her suggestions to improve the manuscript

Comment # 1 Abstract: i)Please provide information on the duration of the H-RP ; ii) Please provide information on the number of events for each outcome variable and iii) whether factors associated with medical events at 30 days were the results of univariate or multivariable analyses. In the conclusion, the result on early start of H-RP is missing.
These comments have been modified in the abstract :
(i) The median [Interquartile range] duration of H-RP was 32 [19 ; 46] days
(ii) The number of events for each outcome variable has been added
(iii) Factors associated with medical events at 30 days were the results of univariate analyses
(iv) We have modified the conclusion as follows: Facing multiple comorbidities and living alone and a long delay before starting the rehabilitation increase the risk of not completing preoperative H-RP.
(v) To respect the 250-word framework, we have removed the univariate factors associated with the risk of non-completion of the program.

Comment # 2 : Strengths and limitations: Please describe the possible effect of selection bias on the results. Please also include this information in the discussion section.
Thank you for your comment, the possible selection bias has been added in the “strengths and limitations” box as follows:
The lack of collection of information regarding refusals to participate means the risk of selection bias cannot be determined.
This point has been also added in the discussion as follows: we did not collect information relating to the number and the reasons for refusal, therefore, we cannot we be sure there was no selection bias.

Comment # 3 : Introduction: Please include percentages for the risk of postoperative complications and rehospitalisation (overall and in fragile patients).
As suggested, this sentence has been added in the introduction
The overall rate of hospital readmissions within 3 months after lobectomy for lung cancer can reach 18% ; in patients with comorbidities, each additional comorbidity was associated with a 2.0% increased probability of readmission. [7] Thomas et al. have shown that underweight patients had a higher surgical complication rate than normal-weight patients (23.2% vs 13.8% $p<0.001$ respectively). [5]

Comment # 3 Methods: A better description of the population is needed (e.g. what is the period of inclusion, how were patients invited to participate in the study, was there any non-response, etc.).

We agree with the reviewer that this section was lacking precision. Here are the elements we have been able to add in the methods section.
All patients were asked to participate by their lung cancer specialist during the appointment when surgery was scheduled. This has been added in the methods section.
On the other hand, we did not collect the number of refusals and the reasons for refusal. Therefore, we cannot provide a precise study flow chart neither can we be sure there was no selection bias. This limitation is reported in the discussion. Finally, the period of inclusion (February 2018 to July 2019) is reported in the results section.

Comment # 4 : Information on details of content and duration of the prehabiliation program is missing (this information could also be displayed in a table).
We thank the reviewer, the median [interquartile range] duration of the prehabilitation program was 32 [19 ; 46] days. This information has been added in the abstract, the results section and Figure 1 with the Odds ratio related to non-completion of the rehabilitation program (OR [IC 95%]: 0.80 [0.22; 2.87], p = 0.73).
Comment # 5 : What were the components of nutritional intervention and how was measured what was needed in each patient?
As mentioned in the methods food fortification advice was provided or oral nutritional supplements were prescribed. The patient's nutritional requirements were assessed by calculating the number of calories received from the 24-h dietary recalls (Willett W, doi:10.1093/oxfordjournals.aje.a114086) and compared to the required amount calculated through the Harris-Benedict equations (ref : Harris JA, Benedit FJ doi:10.1073/pnas.4.12.370)
This has been added in the methods section (with references).
Comment # 6 : How long did training sessions last? Which strength exercises, which coaching, homework exercises? Patients were asked to cycle for 20-40 minutes, but had to reach a minimum of 30 minutes? Did patients fill in a logbook in order to measure completion of components of H-RP?
We thank the reviewer for highlighting the lack of precision of the description in the methods section. We have removed the notion of 20-40 minutes. The participants were instructed to cycle for at least 30 minutes/ session. All participants were asked to complete a logbook to record the exercise sessions carried out.
This has been added in the revised version
Comment # 7 : Were there any barriers with respect to placing a cycle-ergometer at home/room for exercising? And did patients receive a shedule for home-based cycling?
The cycle-ergometer was delivered to the patient's home by a homecare provider technician during a scheduled appointment. All patients had sufficient space within their homes for the device. This has been added in the methods section.
Comment # 7 : Were all patients supervised by the same physiotherapist from the hospital of was supervision performed by regional physiotherapists?
The supervision of patients was carried out by an out-patient physiotherapist located near the patient's home. This has been added in the revised version

Comment # 8 Data collection: 'living situation' is missing;
Thank you this has been added in the revised version
Comment # 9 why did the authors limit postoperative complications to medical events after discharge instead of also including events during hospitalisation? And why did the authors not include duration of hospital stay as important outcome measure?

We fully agree that the length of post-surgical hospitalisation and rate of complications are important outcomes, but our aim was rather to evaluate the events after hospital discharge.

In the revised version, we have added these elements to the results (Table 4).
We have added this sentence in the results section:
Table 4 reports early post-surgical complications (before hospital discharge) and length of hospitalization: neither early post-surgical complications nor the duration of hospitalisation were different in patients who had completed the H-RP compared to those who had not.

Table 4. Early post-surgical complications (before discharge) and length of hospitalization in patients who completed the H-RP versus those who did not.
Variables Patients who completed H-RP
(n = 20)
Patients who did not complete H-RP
(n = 22)
OR (95% CI) p-Value
Pleuro-pulmonary complications, n (%) 12 (60.0) 9 (40.9) 0.46 (0.13 ; 1.59) 0.22
Chest-wall complications, n (%) 1 (5.0) 2 (9.1) 1.90 (0.16 ; 22.71) 0.61
Cardiovascular complications, n (%) 3 (15.0) 3 (13.6) 0.90 (0.16 ; 5.04) 0.90
Neurologic complications, n (%) 1 (5.0) 1 (4.6) 0.91 (0.05 ; 15.49) 0.94
Length of postoperative hospitalisation, days (median, [25th-75th]) 7.5 [6.0 ; 9.5] 7.0 [6.0 ; 12.0] 0.69 (0.20 ; 2.35) 0.56

Comment # 10 : Please include more information on multivariable analyses (forward, backward of stepwise, p-in/p-out). In addition, the multivariable analysis seems to be underpowered.
We agree that the small sample is a risk for the robustness of the model and that the selection of variables remains a challenge. We did not use sequential strategies (forward, stepwise or backward) but we privileged procedure involving all subsets with optimization on the Akaike information criterion
This information was added to the manuscript as follows:
Variables that were associated with the risk of non-completion of the program in the univariate analysis ($p < 0.05$) were used to determine the optimal multivariable regression model (procedure involving all subsets with optimization on lowest Akaike Information Criterion (AIC)) to find the independent variables associated with the risk of non-completion of the program.

Comment # 11 : Given the small sample size, the authors could have used $p<0.10$ for significance.
Given the small sample size, the choice of a $p<0.05$ was to limit the number of variables to be potentially included in the multivariate model; we wanted to keep about 10 observations per variable included (Sauerbrei et al. Statistics in Medecine 2007; 26:5512–5528). In our results, 22 patients did not complete the whole program therefore only 2 or at most 3 variables could be potentially selected for the model
For these two previous comments (variables selection in multivariable model), we are well aware of the limit of our sample size and have clearly underlined this in the limitations section of the study.

Comment # 12 : In the current version of the manuscript, the conclusions/recommendations might be too firm by excluding some factors that might be important with respect to determinants of noncompletion of H-RP and the factors associated with medical events occurring 30-days after hospital discharge.
We fully agree; other factors may have contributed to the risk of non-completion of the programme. Furthermore, as noted in the reviewer's comment #16, we did not collect information on reasons for non-completion or when in the process non-completion occurred.
We therefore propose to mitigate our conclusion as follows:
The presence of multiple comorbidities and living alone were found to be the main obstacles to the completion of a home rehabilitation program. Although other factors of non-completion may not have been identified, these results provide important information for clinicians to identify patients who are at

risk of failure of a home-based program and thus would benefit more from supervised pre-surgical rehabilitation programs.

Comment # 13 : Reference for the modified Borg scale is missing.
The following reference has been added: Reproducibility of Borg scale measurements of dyspnea during exercise in patients with COPD. Mador J et al. Chest 1995;107:1590-7.

Comment # 14 : Results: It is not clear how delays were classified (categorized or continuous variable).
In the logistic regression models, all the variables were categorized (> median versus ≤ median). This has been added in the statistical analysis section.

Comment # 15 : The variable 'delay between program initiation and surgery' seems to be missing in the figures.
As suggested by the reviewer (comment #4), we have added the duration of home rehabilitation program in Figure 1.

Comment # 16 : The manuscript would improve by including information on reasons for non-completion and when in the process non-completion occurred (e.g. first week, last week). In case this information is not available, please include a paragraph in the discussion section.
Unfortunately, this information was not collected. We have added this point within the limits as follows: "Secondly, the criterion on which completion of a rehabilitation program was defined was arbitrary and we did not collect the information on reasons for non-completion and when in the process non-completion occurred".
Furthermore, as proposed in comment #12; our conclusion has been toned down.

Comment # 17 :Tables: Table 2 may clearly state the reasons why participants achieved non-completion; furthermore, how was the completion rate for the full program calculated given the fact that not all patients were referred to all four components of H-RP?

As stated in the response to comment #16, we did not collect the information on reasons for non-completion and when in the process non-completion occurred.
As mentioned, in the methods section (please see "outcomes", Pages 8-9 of the manuscript): Each component achieved was attributed a rating of 25%. The smoking cessation and diet components were automatically rated as 25% if they were unnecessary (i.e. former smoker at inclusion and no nutritional requirements)

To clarify, we have added the following examples in the methods:

Example 1: If at inclusion a patient was 1) non-smoker, 2) did not need nutritional intervention, and during the H-RP achieved at least one supervised physiotherapy session/week and performed at least three home cycle-ergometry sessions/week, therefore the completion rate for the full program was 100%
Example 2: If at inclusion a patient was 1) non-smoker, 2) did not need nutritional intervention, and during the H-RP achieved at least one supervised physiotherapy session/week but performed only one cycle-ergometry sessions/week, therefore the completion rate for the full program was 75%

Comment # 17 :Figures: Please include in the title that results are derived from univariate analyses.
This has been done

Comment # 18 Minor comment: Why is each word in the title capitalized?

This has been modified in the revised version

VERSION 2 – REVIEW

REVIEWER	Catherine Granger The University of Melbourne, Australia
REVIEW RETURNED	25-Nov-2020

GENERAL COMMENTS	Thank you for the opportunity to review the revision of this manuscript. All of my comments have been addressed. I have no further comments and recommend publication.